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(54) Title: X-RAY CONTRAST COMPOSITIONS CONTAINING CELLULOSE DERIVATIVES

(57) Abstract

Disclosed are x-ray contrast compositions for oral or retrograde examination of the gastrointestinal tract comprising an x-ray contrast producing agent in a pharmaceutically acceptable carrier comprising a cellulose derivative.

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X-RAY CONTRAST COMPOSITIONS CONTAINING CELLULOSE DERIVATIVES

This invention relates to x-ray contrast compositions containing contrast agents and cellulose derivatives, and methods for their use in diagnostic radiology of the gastrointestinal tract.

Roentgenographic examination utilizing X-rays and computed tomography (hereinafter CT) scans of fractures and other conditions associated with the skeletal system is routinely practiced without the use of contrast agents. X-ray visualization of organs containing soft tissue, such as the gastrointestinal (hereinafter GI) tract, requires the use of contrast agents which attenuate X-ray radiation. D. P. Swanson et al in "Pharmaceuticals In Medical Imaging", 1990, MacMillan Publishing Company, provide an excellent background in medical imaging utilizing contrast agents.

Roentgenographic examination of the GI tract is indicated for conditions of digestive disorders, changes in bowel habit, abdominal pain, GI bleeding and the like. Prior to radiological examination, administration of a radiopaque contrast medium is necessary to permit adequate delineation of the respective lumen or mucosal surface from surrounding soft tissues. Accordingly, a contrast medium is administered orally to visualize the mouth, pharynx, esophagus, stomach, duodenum and proximal small intestine. The contrast medium is administered rectally for examination of the distal small intestine and the colon.

The most widely used contrast agent for the visualization of the GI tract is barium sulfate administered orally as a suspension or rectally as an enema. (See, for example, U.S. Patent Nos.: 2,659,690;

2,680,089; 3,216,900; 3,235,462; 4,038,379 and 4,120,946). Notwithstanding its relatively good contrast characteristics, negligible absorption from the GI tract following oral or rectal administration and speedy excretion from the body, barium sulfate has certain disadvantages. In the presence of intestinal fluids it lacks homogeneity and adheres poorly to mucus membranes which can result in poor X-ray images. In the colon, when administered as an enema, it flocculates and forms irregular clumps with fecal matter.

Iodinated organic compounds have also been used as GI contrast agents since the iodine atom is an effective X-ray absorber. They have the most versatility and are utilized in the widest variety of procedures. They are very absorptive of X-rays with which the iodine interacts and produce a so-called photoelectric effect which is a large magnification in contrast caused by the photons stopped in the iodine-containing medium. The magnification of contrast exceeds the level that would be expected from relative changes in density. Because of this magnification, relatively low concentrations of the contrast agent can be utilized. (For iodinated agents see, for example, U.S. Patent Nos.: 2,786,055; 3,795,698; 2,820,814; 3,360,436; 3,574,718, 3,733,397; 4,735,795 and 5,047,228.)

The desiderata for an ideal GI contrast agent include: good toxicological profile; the ability to fill the entire bowel/lumen and evenly coat the gut mucosa so that the presence of the bowel is detectable when the lumen is not distended; palatability and nonirritation to the intestinal mucosa; and passage through the GI tract without producing artifacts or stimulating vigorous intestinal peristalsis.

These requirements were addressed by many investigators and their efforts resulted in great improvements over the years. The requirement of evenly coating the gut mucosa with a contrast agent to

effectively cover the walls of the intestines proved to be rather difficult. Without meeting these requirements it is impossible to obtain X-ray pictures of high precision. To that end, the use of certain polymer additives were proposed as illustrated hereunder.

U.S. Patent No. 4,069,306 discloses an x-ray contrast preparation which is said to adhere to the walls of body cavities. The preparation comprises a finely divided water-insoluble inorganic x-ray contrast agent and minute particles of a hydrophilic polymer which is insoluble in water but is water-swellable. The body cavity is supplied with such preparation suspended in water. The x-ray contrast agent is present in admixture with and/or enclosed in and/or adhered to said minute polymer particles.

U.S. Patent No. 4,120,946 discloses a pharmaceutical composition for barium opacification of the digestive tract, comprising colloidal barium sulfate and a polyacrylamide in an aqueous vehicle. The polyacrylamide forms a viscous solution at low concentration which makes it possible to maintain the barium sulfate in suspension and at the same time permit good adherence of the preparation to the walls of the organ which it is desired to x-ray.

U.S. Patent No. 5,019,370 discloses a biodegradable radiographic contrast medium comprising biodegradable polymeric spheres which carry a radiographically opaque element, such as iodine, bromine, samarium and erbium. The contrast medium is provided either in a dry or liquid state and may be administered intravenously, orally and intra-arterially.

Japanese Patent Application No. 55-127322 discloses x-ray contrast compositions containing barium sulfate and a polymeric substance selected from carboxymethyl cellulose salts, propylene glycol alginate, cellulose sulfate polyacrylate, pectin and tragacanth gum. The polymeric substance is used to increase the viscosity of

the compositions.

While these polymeric materials greatly enhance attachment of the contrast agent used therewith to the walls of organs for better visualization thereof, there is still a need for an improved X-ray imaging medium that uniformly coats the soft tissues subjected to diagnostic X-ray examination.

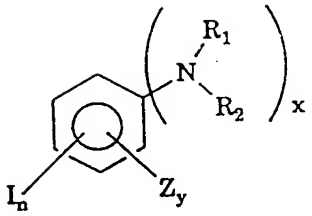
It is the object of the present invention to provide compositions for coating the gastrointestinal tract of mammals to form an effective radiopaque coating thereon by which diagnostic examination of the GI tract may be accomplished. To that end, a thin coating is formed on the inner surface of the GI tract effected by ingesting, prior to visualization by an x-ray emitting device, a cellulose derivative, which has incorporated therein an x-ray contrast agent, capable of coating the GI tract. Such compositions must meet several requirements: both the x-ray contrast agent and the cellulose derivative must be nontoxic; must not contain leachable or digestible components that would deleteriously affect the patient; and no components of the coating should be absorbed by, and pass through, the inner surface of the intestine.

The object of the present invention is achieved by a composition comprising: an x-ray contrast agent in a pharmaceutically acceptable vehicle comprising a cellulose derivative.

In accordance with the invention there is further provided a method for x-ray diagnostic imaging of the GI tract which comprises orally or rectally administering to the patient an effective contrast producing amount of the above-described x-ray contrast compostion.

The x-ray contrast agent of the present invention is selected from:

(1) compounds of the formula:



or a pharmaceutically acceptable salt thereof wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

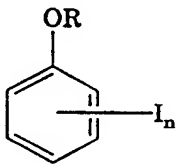
R_1 and R_2 are independently H, C_1-C_{25} alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C_1-C_{25} alkyl, cycloalkyl and halo-lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

n is 1-4;

y is 1-4; and

x is 1 or 2;

(2) compounds of the formula

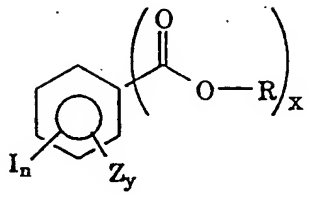


wherein

R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C_1-C_6 alkyl, hydroxy and alkoxy; and

n is 1 to 5;

(3) compounds of the formula



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3{=}CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

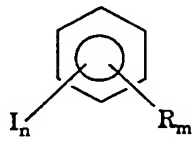
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(4) compounds of the formula



wherein

R is methyl, ethyl, n-propyl, C_4-C_{25} alkyl, cycloalkyl, unsaturated allyl or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy

or lower-alkoxy carbonyl; or $(CR_1R_2)_p$-$(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently H, lower-alkyl, optionally substituted with halo;

n is 2-5;

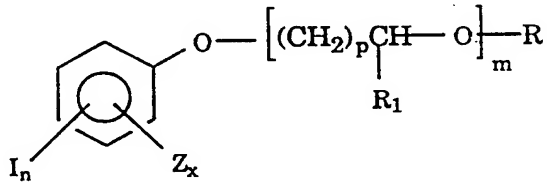
m is 2-5;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

or a pharmaceutically acceptable salt thereof;

(5) compounds of the formula



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, alkoxycarbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl,  or halo-lower-alkyl; each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy-carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-4;

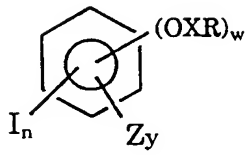
m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

or a pharmaceutically acceptable salt thereof;

(6) compounds of the formula



wherein

X is $-\overset{O}{\overset{\|}{C}}-$ or $-SO_2-$;

Z is H, halo, C_5-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl, aryl or halo-lower-alkyl, each of which may be optionally substituted with lower-alkoxy, hydroxy, carboxy or lower-alkoxy-carbonyl, lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

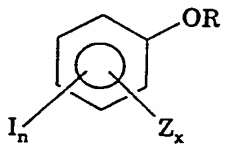
n is 1-5;

y is 0-4; and

w is 1-4;

or a pharmaceutically acceptable salt thereof;

(7) compounds of the formula



or a pharmaceutically acceptable salt thereof

wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C_9-C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy,

hydroxy, carboxy, lower-alkoxy-carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3=CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-5;

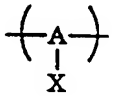
m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(8) a particulate x-ray crystalline contrast agent having a surface modifier adsorbed on the surface thereof;

(9) iodinated polymeric, water-insoluble beads having a particle size of from about 0.01 to about 1000μ wherein said iodinated polymeric beads comprise a polymer containing repeating units of the formula (I)



I

wherein

A is a repeating organic unit in the backbone chain of the polymer; and

X is an organic moiety containing an iodinated aromatic group and a hydrophilic group, said moiety having an iodine content within the range of from about 40 to about 80 weight percent based on the molecular weight of X;

(10) a barium salt.

As used herein, the term halogen (or halo) means fluorine, chlorine, bromine or iodine.

As used herein, the term cycloalkyl means carbocyclic rings having from three to eight ring carbon atoms including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl which may be substituted on any ring carbon atom thereof by one or more lower-alkyl groups, lower-alkoxy groups or halogens.

As used herein the terms lower-alkyl and lower-alkoxy mean monovalent aliphatic radicals, including branched chain radicals, of from one to ten carbon atoms. Thus, the lower-alkyl moiety of such groups include, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl, n-pentyl, 2-methyl-3-butyl, 1-methylbutyl, 2-methylbutyl, neopentyl, n-hexyl, 1-methylpentyl, 3-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 2-hexyl, 3-hexyl, 1,1,3,3-tetramethylpentyl, 1,1-dimethyloctyl and the like.

As used herein, the term lower-alkenyl and lower-alkynyl means monovalent, unsaturated radicals including branched chain radicals of from three to ten carbon atoms and thus include 1-ethenyl, 1-(2-propenyl), 1-(2-butenyl), 1-(1-methyl-2-propenyl), 1-(4-methyl-2-pentenyl), 4,4,6-trimethyl-2-heptenyl, 1-ethynyl, 1-(2-propynyl), 1-(2-butynyl), 1-(1-methyl-2-propynyl), 1-(4-methyl-2-pentynyl) and the like.

As used herein, the term alkylene means divalent saturated radicals, including branched chain radicals of from two to ten carbon atoms having their free valences on different carbon atoms and thus includes 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1-methyl-1, 2-ethylene, 1,8-octylene and the like.

As used herein, the term aryl means an aromatic hydrocarbon radical having six to ten carbon atoms. The preferred aryl groups are phenyl, substituted phenyl and naphthyl substituted by from one to three, the same or different members of the group consisting of lower-alkyl, halogen, hydroxy-lower-alkyl, alkoxy-lower-alkyl and hydroxy.

The x-ray contrast compounds of types (1)-(7) above can comprise one, two, three or four iodine atoms per molecule; preferred species contain at least two, and more preferably, at least three iodine atoms per molecule.

Solid x-ray contrast agents in particulate form useful in the practice of the present invention can be prepared by techniques known in the art. The solid agents are comminuted to the desired size using conventional milling methods, such as airjet or fragmentation milling. We have found that an effective average particle size of less than about 100μ provides for good distribution and coating in the GI tract. As used herein, particle size refers to a number average particle size as measured by conventional techniques, such as sedimentation field flow fractionation and disk centrifugation. An effective average particle size of less than about 100μ means that at least about 90% of the particles have a weight average particle size of less than about 100μ as measured by art recognized techniques.

The cellulose derivatives utilized in the present invention include methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose; and microcrystalline cellulose; having an average particle size of from 0.01 to 100μ, more preferably of from 0.05 to 10μ, and most preferably of 0.1 to 1 μm.

The contrast agent and the cellulose derivative are formulated for administration using physiologically acceptable carriers or excipients in a manner within the skill of the art. The contrast agent and the cellulose derivative with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients are suspended or partially dissolved in an aqueous medium resulting in a dispersion, solution,

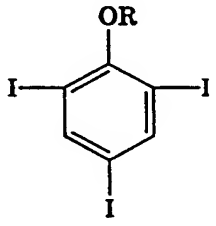
suspension or emulsion.

A method for diagnostic imaging of the GI tract for use in medical procedures in accordance with this invention comprises orally or rectally administering to the mammalian patient in need of x-ray examination, an effective contrast producing amount of a composition of the present invention. After administration, at least a portion of the GI tract containing the administered composition is exposed to x-rays to produce an x-ray image pattern corresponding to the presence of the contrast agent, then the x-ray image is visualized and interpreted using techniques known in the art.

Compounds of type (1) defined above are described in EP-A-613689. For example, N-acetyl-N-2'-octyl-4-iodoaniline and N-(4'-iodophenyl)-2-aminooctane are described therein.

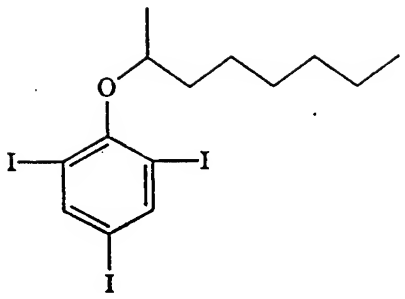
Compounds of type (2) defined above are described in EP-A-568155. For example 2,4,6-triiodophenoxy-2-octane, 2,4,6-triodophenoxy-2-butane, 2,4,6-triodophenoxy-2-hexane and 4-iodophenoxy-2-octane are described therein.

Preferred contrast agents of type (2) have the formula:



wherein R is a secondary alkyl group containing from 4 to 8 carbon atoms.

The most preferred contrast agent of type (2) is the sec-octyl ether of 2,4,6-triiodophenol having the formula:



The contrast agents of type (2) are slightly soluble in water, having a partition coefficient equal or greater than 10. This degree of solubility allows the formation of stable formulations in the form of emulsions and suspensions when the formulations contain the requisite excipients. The term "stable" means that there is no separation of the ingredients contained in the compositions after oral or rectal administration thereof and during radiological examination of the GI tract. The slight solubility of the contrast agents in aqueous media permits diffusion of the contrast agents into the intestinal mucosa and secretions thereby forming a coating on the intestines. On the other hand, due to their slight solubility, the absorption of the contrast agent into the intestinal walls is minimal which reduces the possibility of toxic side effects.

Compounds of type (3) defined above are described in EP-A-614669. For example, 2-octyl-2,3,5-triodobenzoate, 3,3,4,4,5,5,6,6,7,7,8,8-decafluoro-2-octyl-2,3,5-triodobenzoate, bis (2-hexyl)-2,3,5,6-tetraiodo-terephthalate, ethyl 3-(2-octyloxy)-2,4,6-triodobenzoate and bis (2-octyl)-2,4,6-triodo-isophthalate are described therein.

Compounds of type (4) defined above are described in EP-A-609589. For example, 1,3,5-tri-N-hexyl-2,4,6-triiodobenzene, 1,3,5-triethyl-2,4,6-triiodobenzene, 1,3,5-tri-N-butyl-2,4,6-triiodobenzene, 1,3,5-tri-(4-methylpentyl)-2,4,6-triiodobenzene, 1,3,5-tri-N-pentyl-

2,4,6-triiodobenzene, 1,3,5-tri-(3-methylbutyl)-2,4,6-triiodobenzene, 1,3,5-tri-N-propyl-2,4,6-triiodobenzene, 1,3,5-tri-N-heptyl-2,4,6-triiodobenzene, 2-(4-iodophenyl)nonane, 9-(p-iodophenyl)-10-undecenoic acid, ethyl ester and (E)-11-(p-iodophenyl)-9-undecenoic acid, ethyl ester are described therein.

Compounds of type (5) defined above are described in EP-A-614670. For example, the bis-(4-iodophenyl) ether of polyethylene-glycol-400, 1,8-bis-O-(2,4,6-triiodophenyl)-tripropylene glycol, 1,11-bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane, 1,2-bis-(2,4,6-triiodophenoxy)-ethane, the bis-O-(2,4,6-triiodophenyl) ether of polyethylene glycol 400, 1-(3-iodophenoxy)-3,6,9-trioxadecane, 1,3-bis-(2,4,6-triiodophenoxy)-butane, 1-(3-iodophenoxy)-6-(2,4,6-triiodophenoxy)-hexane and 1,12-bis-(2,4,6-triiodophenoxy)-dodecane are described therein.

Compounds of type (6) defined above are described in EP-A-617970. For example, 2,4,6-triiodophenyl 2-ethylhexanoate, 2,4,6-triiodophenyl 2-methylpentanoate, 2,4,6-triiodophenyl 3-cyclopentyl propionate, 2,4,6-triiodophenyl (2-propyl)pentanoate, 2,4,6-triiodophenyl perfluoroheptanoate, 2,4,6-triiodophenyl-tris-(2-ethyl)-hexanoate, 2,4,6-triiodophenyl dodecanoate, 3-trifluoro-methyl-2,4,6-triiodophenyl 2-ethyl hexanoate, 2,4,6-triiodophenyl-bis-(2-methylpentanoate), 2,4,6-triiodophenyl hexanesulfonate, 2,4,6-triiodophenyl heptanesulfonate and 2,4,6-triiodophenyl decanesulfonate are described therein.

Compounds of type (7) defined above are described in EP-A-609587. For example, 2-(4-iodophenoxy)-decane, 2-(2,4,6-triiodophenoxy)-pentadecane, 2-(2,4,6-triiodophenoxy)decane, (2,4,6,-triiodophenoxy)-1H,1H,2H,2H-perflurooctane, 1-(2,4,6-triiodo-3-

trifluorophenoxy)octane, 2-(2,4,6-triiodophenoxy)-nonane, 2-ethyl-1-(2,4,6-triiodophenoxy)-hexane, 3,3-diphenyl-1-(2,4,6-triiodophenoxy)propane, 3-(2,4,6-triiodophenoxy)-nonane, 2-(4-iodophenoxy)-undecane, 2-iodophenoxycyclopentane, 3-iodophenoxycyclopentane, (3,5-dimethyl-2,4,6-triodophenoxy)cyclopentane, 2-(4-iodophenoxy)-pentadecane, 4-iodophenoxycyclopentane, 2,4,6-triiodophenoxycyclopentane, 2,4,6-triiodophenoxy-methylcyclopentane, 2-(2,4,6-triiodophenoxy)ethyl-cyclopentane, (E,E)-1-(2,4,6-triiodophenoxy)-3,7,11-trimethyl-2,6,10-dodecatriene, 1-(2,4,6-triiodophenoxy)-3,7-dimethyl-6-octene, (E)-1-(3,5-dimethyl-2,4,6-triiodophenoxy)-3,7-dimethyl-2,6-octadiene, (E)-1-(2,4,6-triodophenoxy)-3,7-dimethyl-2,6-octadiene, 1-(2,4,6-triiodophenoxy)-3-octyne, 2-(2,4,6-triiodophenoxy)-4-octyne, 1-(2,4,6-triiodophenoxy)-3-octyne, diethyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, diisopropyl 2-(2,4,6-triiodophenoxy)-1,3-propanedioate, ethyl 2,2-bis-(3-iodophenoxy)acetate, ethyl 5-(2,4,6-triiodophenoxy)hexanoate, 5-(2,4,6-triiodophenoxy)-hexan-1-ol, 10-(4-iodophenoxy)-undecan-1-ol, ethyl 5-(2,4,6-triiodophenoxy)hexyl carbonate and ethyl 10-(3-iodophenoxy)-undecanoate are described therein.

Compounds used in the compositions of type (8) defined above are non-radioactive and exist as a discrete, crystalline phase of an organic substance. The crystalline phase differs from an amorphous or non-crystalline phase which results from solvent precipitation techniques such as described in U.S. Patent 4,826,689. The organic substance can be present in one or more suitable crystalline phases. The invention can be practiced with a wide variety of crystalline, non-radioactive x-ray contrast agents. However, the x-ray contrast agent must be poorly soluble and dispersible in at least one liquid medium. By

"poorly soluble", it is meant that the agent has a solubility in the liquid dispersion medium, e.g., water, of less than about 10 mg/ml, and preferably of less than about 1 mg/ml.

The x-ray contrast agent can be an iodinated compound. The iodinated compound can be aromatic or nonaromatic. Aromatic compounds are preferred. The iodinated compound can comprise, one, two, three or more iodine atoms per molecule. Preferred species contain at least two, and more preferably, at least three iodine atoms per molecule. The iodinated compounds selected can contain substituents that do not impart solubility to the compound, such as, for example, alkylureido, alkoxyacylamido, hydroxyacetamido, butyrolactamido, succinimido, trifluoroacetamido, carboxy, carboxamido, hydroxy, alkoxy, acylamino, and the like substituents.

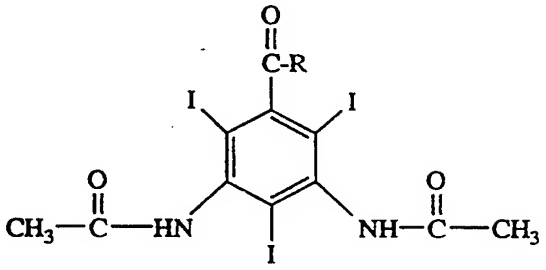
A preferred class of contrast agents includes various esters and amides of iodinated aromatic acids. The esters preferably are alkyl or substituted alkyl esters. The amides can be primary or secondary amides, preferably alkyl or substituted alkyl amides. For example, the contrast agent can be an ester or amide of a substituted triiodobenzoic acid such as an acyl, carbamyl, and/or acylmethyl substituted triiodobenzoic acid. Illustrative representative examples of iodinated aromatic acids include, but are not limited to, diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxaglic acid (hexabrix), ioxitalamic acid, tetraiodoterephthalic acid, iodipamide, icarmic acid, and the like.

Many of the iodinated molecules described above, if in monomeric form, can also be prepared as dimers (sometimes referred to as bis compounds), trimers (sometimes referred to as tris compounds), etc., by techniques known in the art. It is contemplated that this invention can be practiced with poorly soluble-iodinated compounds in monomeric, dimeric, trimeric and

polymeric forms.

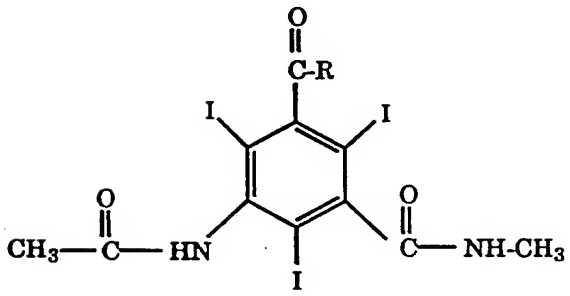
Classes of preferred contrast agents have the following structural formulae:

A.



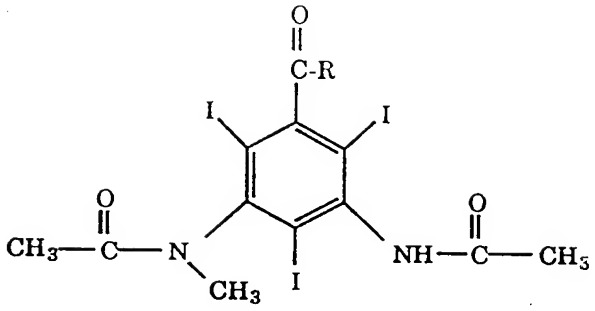
[diatrizoate]

B.

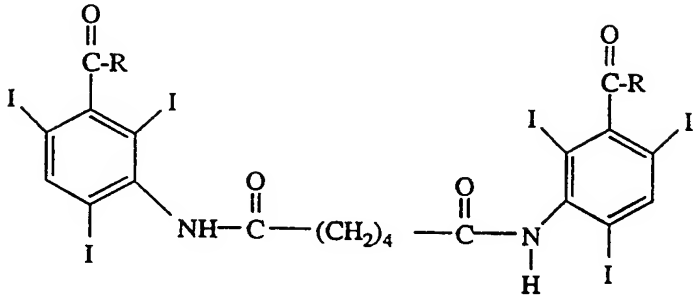


[iothalamate]

C.



D



[iodipamide]

In the above structures R can be OR^1, NR^2R^3, alkylene, -CO.OR^1 or -O-alkylene-CO.OR^1 wherein R^1 is alkyl, and R^2 and R^3 are independently H or alkyl.

Each alkyl group can independently contain from 1-20, preferably 1-8, and more preferably, 1-4 carbon atoms.

The alkylene group preferably contains from 1 to 4 carbon atoms such as methylene, ethylene, propylene and the like.

Particularly preferred contrast agents include the ethyl ester of diatrizoic acid, i.e., ethyl 3,5-diacetamido-2,4,6-triiodobenzoate, also known as ethyl 3,5-bis(acetylamino)-2,4,6-triodobenzoate or ethyl diatrizoate, having the structural formula A above wherein R=-OCH_2CH_3; the ethyl glycolate ester of diatrizoic acid, i.e., ethyl (3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)acetate, also known as ethyl diatrizoxyacetate; and ethyl 2-(3,5-bis(acetylamino)-2,4,6-triiodobenzoyloxy)butyrate, also known as ethyl 2-diatrizoxybutyrate.

In addition, the invention can be practiced in conjunction with the water insoluble iodinated carbonate esters described in PCT/EP90/00053.

The above described x-ray contrast agents are known compounds and/or can be prepared by techniques known in the art. For example, water-insoluble esters and terminal amides of acids such as the above-described iodinated aromatic acids can be prepared by conventional alkylation or amidation techniques known in the art. The above-noted acids and other acids which can be used as starting materials are commercially available and/or can be prepared by techniques known in the art.

The particles useful in the compositions of type (8) defined above include a surface modifier. Surface modifiers useful herein physically adhere to the surface of the x-ray contrast agent but do not chemically react with the agent or itself. Individually adsorbed

molecules of the surface modifier are essentially free of intermolecular crosslinkages. Suitable surface modifiers can be selected from known organic and inorganic pharmaceutical excipients such as various polymers, low-molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of surface modifiers include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g. macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxamers such as Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, and poloxamines such as Tetronic 908 (also known as Poloxamine 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene

oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 80, which is a polyoxyethylene sorbitan fatty acid ester, available from ICI Specialty Chemicals, and Carbowax 3350 and 934, which are polyethylene glycols available from Union Carbide. Surface modifiers which have been found to be particularly useful include Tetronic 908, the Tweens, Pluronic F-68 and polyvinylpyrrolidone.

Other useful surface modifiers include:

decanoyl-N-methylglucamide;

n-decyl β-D-glucopyranoside;

n-decylβ-D-maltopyranoside;

n-dodecyl β-D-glucopyranoside;

n-dodecyl β-D-maltoside;

heptanoyl-N-methylglucamide

n-heptyl β-D-glucopyranoside;

n-heptyl β-D-thioglucoside;

n-hexyl β-D-glucopyranoside;

nonanoyl-N-methylglucamide;

n-nonyl β-D-glucopyranoside;

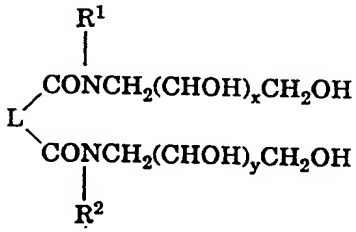
octanoyl-N-methylglucamide;

n-octyl β-D-glucopyranoside;

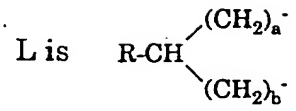
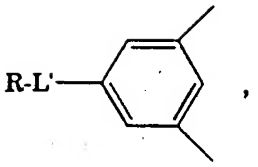
octyl β-D-thioglucopyranoside;

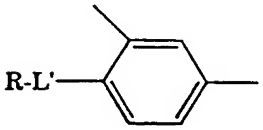
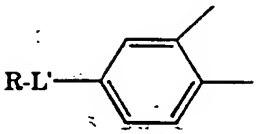
and the like.

A particularly preferred class of surface modifiers includes water-soluble or water-dispersible compounds having the formula



wherein

L is  ,  ,

 or 

L' is a chemical bond, -O-, -S-, -NH-, -CONH- or -SO_2NH-;

R is a hydrophobic substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, or a substituted or unsubstituted aryl group;

each of R^1 and R^2 independently is hydrogen or an alkyl group having from 1 to 4 carbon atoms;

each of a and b independently is 0 or an integer from 1 to 3, provided that the sum of a and b is not greater than 3; and,

each of x and y independently is an integer from 3 to 7.

Preferred compounds within this class conform to the above structure wherein R contains from 6 to 36 carbon atoms, for example, R is an n-alkyl group containing from 6 to 18 carbon atoms, each of R^1 and R^2 independently is a methyl, ethyl, propyl or butyl group and a is 0 and b is 0. This class of surface modifiers is described in U.K. Patent Application No. 9104957.7 filed March 8, 1991 and can be prepared by reacting an appropriate dicarboxylic acid ester with an appropriate monosaccharide amine, preferably in the absence of a solvent, at a reaction temperature from 140 to 200°C.

The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in

combination.

The particles useful in the compositions of type (8) defined above can be prepared in accordance with the wet grinding process described in U.S. Patent No. 5,145,684. The process comprises dispersing a poorly soluble x-ray contrast agent in a liquid dispersion medium and wet-grinding the agent in the presence of grinding media to reduce the particle size of the contrast agent to an effective average particle size of from about 0.05 μ to about 100 μ, preferably of from about 0.05 μ to about 5 μ and most preferably from about 0.1 μ to about 1 μ. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

As used herein, particle size refers to a number average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation. By "an effective average particle size of from about 0.05 μ to about 100 μ" is meant that at least 90% of the particles have a weight average particle size of from about 0.05 μ to about 100 μ when measured by the above-noted techniques. The particle size range allows sufficient number of particles' distribution in the film forming composition when the GI tract is coated therewith, yet insures against absorption through the intestinal walls.

The water-insoluble iodinated polymeric beads utilized in the compositions of type (9) defined above are disclosed in U. S. Patent No. 4,406,878 and also in WO94/25075.

The general structural formula of iodinated polymers of the invention is represented by structural formula I above. The backbone chain of the iodinated

polymer can represent:

(i) a condensation polymer such as a polyester, polyamide, polyurethane, polycarbonate, polyepoxide, polyether, a phenol-formaldehyde polymer and equivalent condensation polymers;

(ii) an addition polymer produced by the polymerization of one or more addition polymerizable monomers containing a polymerizable unsaturated double bond, e.g., vinyl monomers, including such addition polymers as poly(vinyl alcohol), poly(alkylmethacrylates), poly(alkylacrylates), and equivalent addition polymers; or

(iii) a naturally occurring polymer, for example, a polysaccharide containing repeating glucose units such as starch, glycogen, cellulose, cellulosic derivatives, and equivalent naturally occuring polymers.

Preferably, repeating units A of formula I represent the residue of a repeating unit having an appended hydroxyl group, such as the repeating unit of poly (vinyl alcohol), the repeating epoxy unit of a polyepoxide, the repeating unit of a hydroxylated acrylic polymer such as poly (hydroxyethylacylate), or the repeating glucose unit of a naturally occurring polysaccharide. The appended hydroxyl group can serve either as a crosslinking site or as a reaction site for precursor compounds of the organic moiety X in formula I. Such precursor compounds can be chemically linked to the repeating units of the polymer backbone chain through a condensation reaction with the appended hydroxy group.

The organic moiety X of formula I above represents an iodine-containing organic fragment comprising an iodinated aromatic group and one or more hydrophilic groups. To obtain the high iodine content characteristic of the polymers used in the invention, the iodinated aromatic group have multiple iodine substituents bonded directly to the aromatic carbon ring

atoms. Especially preferred among these iodinated aromatic groups are aromatic groups containing three, preferably four, carbon ring atoms substituted by iodine. A preferred iodinated aromatic group is an iodinated phenyl ring, although napthyl rings and nitrogen-containing heterocyclic rings containing 5 to 7 ring atoms can also be used. An especially preferred iodinated aromatic group is a phenyl ring bearing iodine substituents on a 4 of the carbon ring atoms.

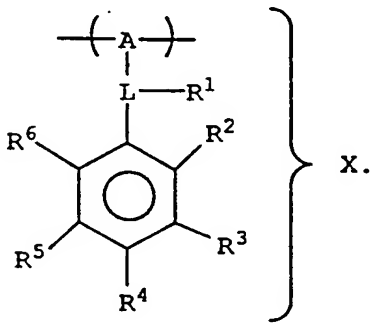
The hydrophilic group(s) of X are typically present as a substituent(s) bonded directly, or indirectly through a chemical linking group, to one or more of the carbon ring atoms of the iodinated aromatic group. Preferred linking groups include short chain aliphatic groups, e.g., alkylene groups, amido groups and equivalent aliphatic groups, having 1 to 4 carbon atoms. Typically hydrophilic groups can be selected from a variety of such groups including carboxyl groups; sulfo groups; amino groups; salts thereof such as carboxylate salts, sulfonate salts, ammonium salts; polyols such as glucose groups; and equivalent hydrophilic groups.

Typically, the precursors from which the organic moiety X of formula I is derived contains a reactive group which forms a chemical linking group with the repeating unit of the polymer backbone chain. In the preferred embodiment of the invention wherein the repeating unit of the polymer backbone chain represents the residue of a repeating unit bearing a hydroxyl group, the reactive group contained on the precursor of X is a group reactive with the hydroxy group. For example, the reactive group can be a carboxyl group which condenses with the appended hydroxy group of the backbone chain to form an ester group linking an iodinated aromatic moiety of the polymer backbone. A variety of other reactive groups which react with a hydroxy group to form such chemical linking groups as ethers, amides, thioesters, carbonates, carbamates,

sulfides, and equivalents, can also be used.

A partial listing of precursors for the moiety X of formula I includes, for example, 3-(3-amino-2,4,6-triiodophenyl)-2-ethylpropionic acid; 3-(3-hydroxy-2,4,6-triiodophenyl)-2-ethylpropionic acid; sodium 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethylacrylate; 3,5-diiodo-4-pyridone-N-acetic acid; 3-acetamido-2,4,6-triiodobenzoic acid; tetraiodophthalic anhydride; and the like. Tetraiodophthalic anhydride can be particularly useful because of its high iodine content.

Based on the foregoing description, a structural formula of certain preferred iodinated polymers can be illustrated as



wherein:

A is as defined in formula I above;

X is as defined in formula I above;

L represents one of the above-described linking groups, e.g. ester, ether, amide, thioester, carbonate, carbamate, sulfide and the like; and each of R^1 to R^6 which may be the same or different, represents hydrogen, an iodine-containing substituent, or a hydrophilic group-containing substituent, with the proviso that the iodine content of X is from about 40 to 80 percent (based on the molecular weight of X).

Preferred iodinated polymers are crosslinked. This can enhance the water-insolubility and resistance to swell properties of the polymer. Crosslinking can be effected by incorporation of suitable crosslinking sites either on the polymer backbone chain or on the moiety X

or both. For example, in a preferred embodiment wherein the polymer contains a repeating backbone unit bearing an appended hydroxyl group and a sidechain group A containing a carboxyl group as a hydrophilic group, a hydroxyl group appended to the backbone chain of one polymer can react with the carboxyl group attached to the sidechain X of another polymer, thereby crosslinking the two polymers through an ester linkage.

The polymeric contrast agents of the invention contain both hydrophilic and hydrophobic groups. Repeating backbone units A of formula I are substantially hydrophobic as are many portions of the moiety X. Of course X also contains one or more hydrophilic groups. This combination of hydrophobic and hydrophilic groups is believed important to provide the proper polymer surface and electrical characteristics which, in turn, provide proper polymer compatibility with body organs and tissues.

The iodinated polymers can be prepared by any of a variety of conventional polymerization and chemical reaction techniques. A preferred reaction sequence is to chemically react precursor compounds for the side-chain group X with a preformed polymer containing appended groups serving as suitable reaction sites, e.g., hydroxyl groups. The preformed polymer can be prepared by addition or condensation polymerization, depending on the polymer; or it can be obtained from naturally occurring sources in the case of naturally occurring polymers; e.g., polysaccharides. The precursor compounds for the moiety X can be reacted with the reaction site on the polymer backbone by a variety of well-known reaction procedures, depending on the nature of the linking group L in formula II above which is formed in this reaction. Advantageously, the reaction of these precursor compounds is carried out under emulsifying conditions so that the resultant polymers are obtained in finely-divided particulate

form. Crosslinking can be carried out during or following attachment of the moiety X of the polymer backbone.

An example of a polymer based on poly(vinyl alcohol) and tetraiodophthalic acid is described in WO94/25075 mentioned above.

Having obtained a water-insoluble and non-water-swellable iodinated polymer as described above, the polymer can be subjected to grinding or milling treatment to obtain polymer particles of the appropriate size range. Of course, in cases where the polymers are prepared under suitable conditions, such as bead polymerization or emulsifying conditions, the polymers may already have an appropriate particle size so that additional milling or grinding may be unnecessary. A useful particle size for these polymer particles is within the range of from about 0.01 to 1000 microns , preferably 0.1 to 100 microns.

The preferred barium salt (the contrast agent of type (10) mentioned above) is barium sulfate which is a white, radiopaque, crystalline powder that is essentially insoluble in water. It is commercially available in the particle size range of 0.001 to 0.1 micron diameter. However, good results are obtainable with other finely-divided, inorganic, essentially water-insoluble salts of barium including barium hexaboride, barium chromite, barium fluogallate, barium tri-ortho phosphate, barium metasilicate, barium titanate, barium zirconate and zirconium oxide. The compositions of the present invention contain from about 5% w/w to about 95% w/w of the barium salt. The compositions may be in the form of dispersions, colloids or suspensoids, however, we prefer to use colloids as the preferred embodiment.

The contrast agents used in the invention may be formulated for administration using physiologically

acceptable carriers or excipients in a manner within the skill of the art. The compounds with the addition of pharmaceutically acceptable aids (such as surfactants and emulsifiers) and excipients may be suspended or partially dissolved in an aqueous medium resulting in a dispersion, solution or suspension. However, the oily contrast agents are preferably made into emulsions.

Compositions of the present invention utilising contrast agents of types (1) to (8) defined above comprise the following pharmaceutically acceptable components based on % w/v:

Ingredients	Broad Range	More Preferred Range	Most Preferred Range
Contrast agent (mg I/ml of total suspension)	30 - 200	40 - 160	85 - 120
Cellulose derivative (% w/v)	0.05 - 10	0.1 - 4	0.2 - 1
Oily Vehicle (%w/v)	0.0 - 55	0.1 - 25	7 - 15
Surfactant (% w/v)	0.0 - 20	0.1 - 10	3 - 7
Viscosity modifying excipients (% w/v)	0.0 - 15	0.001 - 4	0.05 - 1

Water - q.s. to 100% by volume

Compositions of the present invention utilising contrast agents of type (9) defined above comprise the following pharmaceutically acceptable components based on % w/v:

Ingredients	Broad Range	Preferred Range
Iodinated Polyeric Beads (% w/v)	5 - 95	20 - 70
Cellulose derivative (% w/v)	0.05 - 10	0.1 - 4
Surfactant (% w/v)	0.1 - 20	3 - 7
Viscosity modifying excipients (% w/v)	0.001 - 4	0.05 - 1

Water - q.s. to 100% by volume

Compositions of the present invention utilising barium salts comprise the following pharmaceutically acceptable components based on % w/v:

Ingredients	Broad Range	Preferred Range
Barium Salt (w/v)	5 - 95	40 - 70
Cellulose derivative (% w/v)	0.1 - 10	0.2 - 1
Oily Vehicle (% w/v)	0.1 - 55	7 - 15
Surfactant (% w/v)	0.1 - 20	3 - 7
Viscosity modifying excipients (% w/v)	0.001 - 15	0.05 - 1

Water - q.s. to 100% by volume

When the composition is used for CT imaging of the GI tract, the concentration of the x-ray contrast agent should be in the range of from 0.01 to 40 mg I/ml, more preferably of from 0.25 to 25 mg I/ml and most preferably of from 4-12 mg I/ml.

The preferred cellulose derivative utilized in the present invention is AVICEL® RC-591, which is a mixture of about 89 parts microcrystalline cellulose and about 11 parts of sodium carboxymethylcellulose.

In further reference to the components used in the

compositions of the present invention the following should be noted.

The x-ray contrast agent present in concentrations lower than the above-stated minimum in formulations does not provide good quality x-ray or CT images, while concentrations above the maximum concentration render the GI tract too radiopaque and do not allow sufficient delineation of the GI tract.

In practicing the present invention an oil-in-water emulsion is preferred over a water-in-oil emulsion, suspension and dispersion. Oily materials, the density of which approximate the density of the aqueous phase impart stability to emulsions. For that reason low density oils, such as mineral oils, are desirable in preparing the emulsions. When the x-ray contrast agents are oily substances at room temperature, the presence of an additional oily vehicle is not always necessary. Above about 55% w/v of oil the emulsion is no longer an oil-in-water emulsion but shifts to a water-in-oil emulsion.

Compositions without the presence of surfactants still provide excellent x-ray images, however, without surfactants the compositions are very difficult to emulsify and only suspensions/dispersions are produced which are less desirable for coating the GI tract and are also less stable on shelf-life. For reason of toxicity it is desirable to keep the concentration of certain surfactants as low as possible; above about 20% w/v the risk of toxicity rapidly increases.

While the various types of compounds used in the present invention in formulations with a pharmaceutically acceptable vehicle provide good quality x-ray images, the addition of a cellulose derivative to the formulations greatly increases the quality of the x-ray images. At the low extreme of the concentration range there is little or no benefit gained, while above the higher extreme of the concentration range the

emulsion is too viscous for administration.

Depending on the form and amount of cellulose derivative used, additions of viscosity modifying agents may not be necessary; at higher levels than about 15% w/v the viscosity is too high and gels will tend to form.

The following formulation examples will further illustrate the invention

Example 1

Components	Amounts in % w/v
N-acetyl-N-2-octyl-4-iodoaniline	17.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 2

Components	Amounts in % w/v
N-(4'-iodophenyl)-2-amino octane (oil at room temperature)	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 3

Components	Amounts in % w/v
2,4,6-Triiodophenoxy-2-octane	14.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 4

Components	Amounts in % w/v
2,4,6-Triiodophenoxy-2-butane	17.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 5

Components	Amounts in % w/v
2,4,6-Triiodophenoxy-2-hexane	25.40
AVICEL® RC-591	10.00
q.s. with water to 100% by volume	

Example 6

Components	Amounts in % w/v
4-Iodophenoxy-2-octane	30.00
Light Mineral Oil, NF	20.50
Polysorbate 80 (Tween 80)	3.00
AVICEL® RC-591	0.15
q.s. with water to 100% by volume	

Example 7

Components	Amounts in % w/v
2-Octyl-2,3,5-triiodobenzoate	17.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 8

Components	Amounts in % w/v
3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluoro-2-octyl-2,3,5-triiodobenzoate	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 9

Components	Amounts in % w/v
1,3,5-Tri-N-hexyl-2,4,6-triiodobenzene	17.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 10

Components	Amounts in % w/v
1,3,5-Triethyl-2,4,6-triiodobenzene (oil at room temperature)	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 11

Components	Amounts in % w/v
1,3,5-Tri-N-butyl-2,4,6-triiodobenzene	20.00
Light Mineral Oil, NF	5.00
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 12

Components	Amounts in % w/v
2,(4-Iodophenyl) nonane	25.00
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.75
q.s. with water to 100% by volume	

Example 13

Components	Amounts in % w/v
Bis-(4-iodophenyl)ether of polyethylene glycol-400	17.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 14

Components	Amounts in % w/v
1,8-Bis-O-(2,4,6-triiodophenyl)-tripropylene glycol (oil at room temperature)	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 15

Components	Amounts in % w/v
1,11-Bis-(2,4,6-triiodophenoxy)-3,6,9-trioxaundecane	17.50
Light Mineral Oil, NF	12.50
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50

AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 16

Components	Amounts in % w/v
1-(3-Iodophenoxy)3,6,9-Trioxadecane	25.00
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 17

Components	Amounts in % w/v
2,4,6-Triiodophenyl 2-ethylhexanoate	17.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 18

Components	Amounts in % w/v
2,4,6-Triiodophenyl-tris-(2-ethylhexanoate)	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 19

Components	Amounts in % w/v
2,4,6-Triiodophenyl-3-cyclopentyl propionate	20.00

Light Mineral Oil, NF	12.50
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 20

Components	Amounts in % w/v
3-Trifluoromethyl-2,4,6-triiodophenyl-tris-(2-ethylhexanoate)	20.00
Polysorbate 20 (Tween 20)	5.00
AVICEL® RC-591	1.00
q.s. with water to 100% by volume	

Example 21

Components	Amounts in % w/v
2,4,6-Triiodophenyl hexanesulfonate	20.00
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	2.00
Sorbitan Mono-oleate (Span 80)	1.00
AVICEL® RC-591	1.00
q.s. with water to 100% by volume	

Example 22

Components	Amounts in % w/v
2,4,6-Triiodophenoxymethylcyclopentane	14.50
Light Mineral Oil, NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% volume	

Example 23

Components	Amounts in % w/v
2-(4-Iodophenoxy)pentadecane	17.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% volume	

Example 24

Components	Amounts in % w/v
2-Iodophenoxycyclopentane	25.20
Light Mineral Oil, NF	20.50
Polysorbate 80 (Tween 80)	3.00
AVICEL® RC-591	0.15
q.s. with water to 100% volume	

Example 25

Components	Amounts in % w/v
Ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate	17.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 26

Components	Amounts in % w/v
Ethyl (3,5-bis(acetylamino)-2,4,6-triiodo-benzoyloxy)acetate	25.00
Light Mineral Oil, NF	10.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 27

Components	Amounts in % w/v
Ethyl 2-(3,5-bis(acetylamino)-2,4,6-triiodo-benzoyloxy)butyrate	30.00
Pluronic F-68	10.00
AVICEL® RC-591	2.00
q.s. with water to 100% by volume	

Example 28

Components	Amounts in % w/v
Ethyl 3,5-bis(acetylamino)-2,4,6-triiodobenzoate	17.50
Light Mineral Oil NF	12.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 29

Components	Amounts in % w/v
Iodinated Polymeric Beads	17.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 30

Components	Amounts in % w/v
Iodinated Polymeric Beads	25.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 31

Components	Amounts in % w/v
Iodinated Polymeric Beads	20.00
Polysorbate 20 (Tween 20)	5.00
AVICEL® RC-591	1.00
q.s. with water to 100% by volume	

Example 32

Components	Amounts in % w/v
Iodinated Polymeric Beads	30.00
Mineral Oil, NF	10.00
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 33

Components	Amounts in % w/v
Barium Sulfate	17.50
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 34

Components	Amounts in % w/v
Barium Hexaboride	25.00
Light Mineral Oil, NF	9.50
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	6.50
q.s. with water to 100% by volume	

Example 35

Components	Amounts in % w/v
Barium Chromite	70.00
Light Mineral Oil, NF	5.00
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 36

Components	Amounts in % w/v
Barium Metasilicate	85.00
Polysorbate 20 (Tween 20)	2.50
Sorbitan Mono-laurate (Span 20)	2.50
AVICEL® RC-591	0.75
q.s. with water to 100% by volume	

Example 37

Components	Amounts in % w/v
Barium Fluogallate	50.00
Mineral Oil, NF	10.00
Polysorbate 80 (Tween 80)	3.37
Sorbitan Mono-oleate (Span 80)	1.64
AVICEL® RC-591	0.50
q.s. with water to 100% by volume	

Example 38

Components	Amounts in % w/v
Barium Tri-orthophosphate	60.00
Polysorbate 80 (Tween 80)	5.00
AVICEL® RC-591	2.00
q.s. with water to 100% by volume	

As known by those skilled in the art, surfactants or emulsifiers can reduce the interfacial tension between two immiscible phases, i.e., oil-in-aqueous medium. These agents can be used alone or in combination with other emulsifying agents and surfactants. For example, Dow Corning Medical Antifoam AF, which is a composition of 30% w/v polydimethylsiloxane simethicone and silica aerogel, 14% w/v stearate emulsifiers and 0.075% w/v sorbic acid, the balance being water, may be used by itself. Intralipid, which is an emulsion of fatty acids needs the presence of a suspending agent for it to form an acceptable emulsion with contrast agents of the present invention. The surface active agents may be cationic, anionic, nonionic, zwitterionic or a mixture of two or more of these agents.

Suitable cationic surfactants include cetyl trimethyl ammonium bromide. Suitable anionic agents include sodium lauryl sulphate, sodium heptadecyl sulphate, alkyl benzenesulphonic acids and salts thereof, sodium butylnapthalene sulfonate, and sulphosuccinates. Zwitterionic surface active agents are substances that when dissolved in water they behave as diprotic acids and, as they ionize, they behave both as a weak base and a weak acid. Since the two charges on the molecule balance each other out the molecules act as neutral molecules. The pH at which the zwitterion concentration is maximum is known as the isoelectric point. Compounds, such as certain amino acids having an isoelectric point at the desired pH of the formulations of the present invention are useful in practicing the present invention.

In preparing the formulations of the present invention we prefer to use nonionic emulsifiers or surface active agents which, similarly to the nonionic contrast agents, possess a superior toxicological profile to that of anionic, cationic or zwitterionic

agents. In the nonionic emulsifying agents the proportions of hydrophilic and hydrophobic groups are about evenly balanced. They differ from anionic and cationic surfactants by the absence of charge on the molecule and, for that reason, are generally less of an irritant than the cationic or anionic surfactants. Nonionic surfactants include carboxylic esters, carboxylic amides, ethoxylated alkylphenols and ethoxylated aliphatic alcohols.

One particular type of carboxylic ester nonionic surface active agents are the partial, for example monoesters formed by the reaction of fatty and resin acids, for example of about 8 to about 18 carbon atoms, with polyhydric alcohols, for example glycerol, glycols such as mono-, di-, tetra- and hexaethylene glycol, sorbitan, and the like; and similar compounds formed by the direct addition of varying molar ratios of ethylene oxide to the hydroxy group of fatty acids.

Another type of carboxylic esters is the condensation products of fatty and resin partial acids, for example mono-, esters ethylene oxide, such as fatty or resin acid esters of polyoxyethylene sorbitan and sorbitol, for example polyoxyethylene sorbitan, monotall oil esters. These may contain, for example, from about 3 to about 80 oxyethylene units per molecule and fatty or resin acid groups of from about 8 to about 18 carbon atoms. Examples of naturally occurring fatty acid mixtures which may be used are those from coconut oil and tallow while examples of single fatty acids are dodecanoic acid and oleic acid.

Carboxylic amide nonionic surface active agents are the ammonia, monoethylamine and diethylamine amides of fatty acids having an acyl chain of from about 8 to about 18 carbon atoms.

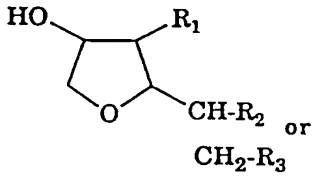
The ethoxylated alkylphenol nonionic surface active agents include various polyethylene oxide condensates of alkylphenols, especially the condensation products of

monoalkylphenols or dialkylphenols wherein the alkyl group contains about 6 to about 12 carbon atoms in either branched chain or particularly straight chain configuration, for example, octyl cresol, octyl phenol or nonyl phenol, with ethylene oxide, said ethylene oxide being present in amounts equal to from about 5 to about 25 moles of ethylene oxide per mole of alkylphenol.

Ethoxylated aliphatic alcohol nonionic surface active agents include the condensation products of aliphatic alcohols having from about 8 to 18 carbon atoms in either straight chain or branched chain configuration, for example oleyl or cetyl alcohol, with ethylene oxide, said ethylene oxide being present in equal amounts from about 30 to about 60 moles of ethylene oxide per mole of alcohol.

Preferred nonionic surface active agents include:

Sorbitan esters (sold under the trade name Span) having the formula:



wherein

$R_1 = R_2 = OH$, $R_3 = R$ for sorbitan monoesters,
$R_1 = OH$, $R_2 = R_3 = R$ for sorbitan diesters,
$R_1 = R_2 = R_3 = R$ for sorbitan triesters,
where R = $(C_{11}H_{23})COO$ for laurate,
$(C_{17}H_{33})COO$ for oleate,
$(C_{15}H_{31})COO$ for palmitate,
$(C_{17}H_{35})COO$ for stearate.

Polyoxyethylene alkyl ethers (i.e. Brijs) having the formula:

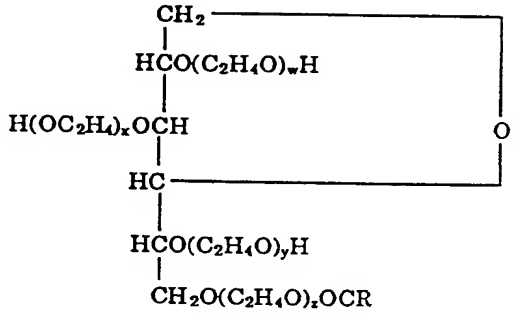
$$CH_3(CH_2)_x(O\text{-}CH_2\text{-}CH_2)_yOH$$

where (x + 1) is the number of carbon atoms in the alkyl chain, typically:

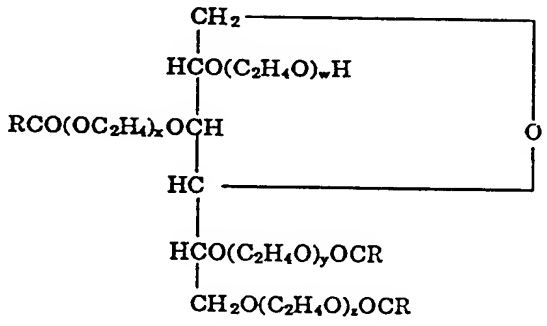
12	lauryl	(dodecyl)
14	myristyl	(tetradecyl)
16	cetyl	(hexadecyl)
18	stearyl	(octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain, typically 10-60.

Polyethylene sorbitan fatty acid esters, sold under the trade names of Polysorbates 20, 40, 60, 65, 80 & 85, having the formulae (1) and (2)



(1)



(2)

wherein

w+x+y+z = 20 (Polysorbate 20, 40, 60, 65, 80 and 85)

w+x+y+z = 5 (Polysorbate 81)
w+x+y+z = 4 (Polysorbate 21 and 61).

Polyethylene stearates, such as:
poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxyoctadecanoate;
polyethylene glycol monostearate; and
poly(oxy-1,2-ethanediyl)-α-(1-oxooctadecyl)-ω-hydroxy-polyethylene glycol monostearate.

The dosages of the contrast agent used according to the method of the present invention will vary according to the precise nature of the contrast agent used. Preferably, however, the dosage should be kept as low as is consistent with achieving contrast enhanced imaging. By employing as small amount of contrast agent as possible, toxicity potential is minimized. For most contrast agents of the present invention dosages will be in the range of from about 0.1 to about 16.0 g iodine/kg body weight, preferably in the range of from about 0.5 to about 6.0 g iodine/kg of body weight, and most preferably, in the range of from about 1.2 to about 2.0 g iodine/kg body weight for regular x-ray visualization of the GI tract. For CT scanning, the contrast agents of the present invention will be in the range of from about 1 to about 600 mg iodine/kg body weight, preferably in the range of from about 20 to about 200 mg iodine/kg body weight, and most preferably in the range of from about 40 to about 80 mg iodine/kg body weight.

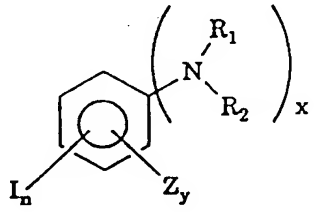
The concentration of the contrast agent should be in the range of from about 0.001% w/v to about 75% w/v of the formulation, preferably from about 0.05% w/v to about 50% w/v and most preferably of from about 0.1 % w/v to about 20% w/v.

CLAIMS:

1. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising:

(a) an x-ray contrast agent selected from

(1) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

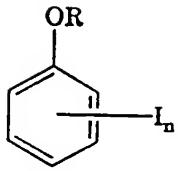
R_1 and R_2 are independently H, C_1-C_{25} alkyl, cycloalkyl, acetyl or halo-lower-alkyl, wherein said C_1-C_{25} alkyl, cycloalkyl and halo-lower-alkyl are optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy and said acetyl is optionally substituted with fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, lower-alkoxy carbonyl or lower-alkoxy-carbonyloxy;

n is 1-4;

y is 1-4; and

x is 1 or 2;

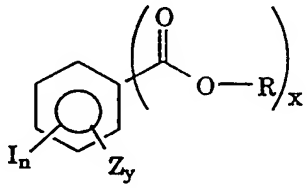
(2) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

R is a substituted or unsubstituted alkyl group containing from 2 to 8 carbon atoms, wherein said substituents are selected from the group consisting of C_1-C_6 alkyl, hydroxy and alkoxy; and n is 1 to 5;

(3) from about 0.01 to 200 mg of iodine per ml of the compositon of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy-carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3{=}CR_4)_m$Q, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-3

y is 1-4;

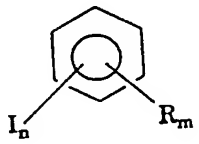
n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(4) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

R is methyl, ethyl, n-propyl, C_4-C_{25} alkyl, cycloalkyl, unsaturated allyl or halo-lower-alkyl, each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy or lower-alkoxy-carbonyl; or $(CR_1R_2)_p$-$(CR_3{=}CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently H, lower-alkyl, optionally substituted with halo;

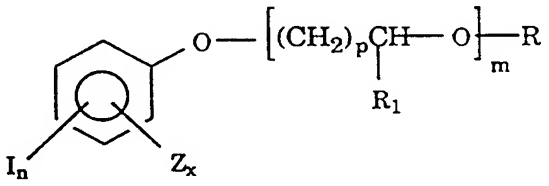
n is 2-5;

m is 2-5;

p is 1-10; and

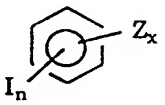
Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(5) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, alkoxycarbonyl, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl,  or halo-lower-alkyl; each of which may be optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy-carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3{=}CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently H or lower-alkyl, optionally substituted with halo;

x is 1-4;

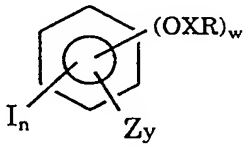
n is 1-4;

m is 1-15;

p is 1-20; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(6) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

X is  or $-SO_2-$

Z is H, halo, C_5-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is C_1-C_{25} alkyl, cycloalkyl, aryl or halo-lower-alkyl, each of which may be optionally substituted with lower-alkoxy, hydroxy, carboxy or lower-alkoxy carbonyl,

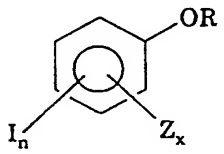
lower-alkenyl, lower-alkynyl, lower-alkylene or lower-alkoxy-carbonyloxy;

n is 1-4;

m is 0.4; and

w is 1-4;

(7) from about 0.01 to 200 mg of iodine per ml of the composition of an x-ray contrast producing agent having the formula, or a pharmaceutically acceptable salt thereof



wherein

Z is H, halo, C_1-C_{20} alkyl, cycloalkyl, lower alkoxy, cyano, where the alkyl and cycloalkyl groups can be substituted with halogen or halo-lower-alkyl groups;

R is methyl, ethyl, propyl, C_9-C_{25} alkyl, cycloalkyl, or halo-lower-alkyl, optionally substituted with halo, fluoro-lower-alkyl, aryl, lower-alkoxy, hydroxy, carboxy, lower-alkoxy-carbonyl or lower-alkoxy-carbonyloxy; or $(CR_1R_2)_p$-$(CR_3{=}CR_4)_mQ$, or $(CR_1R_2)_p$-C≡C-Q;

R_1, R_2, R_3 and R_4 are independently lower-alkyl, optionally substituted with halo;

x is 1-4;

n is 1-5;

m is 1-15;

p is 1-10; and

Q is H, lower-alkyl, lower-alkenyl, lower-alkynyl, lower-alkylene, aryl, or aryl-lower-alkyl;

(b) from 0.05 to 10% w/v of a cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl

methylcellulose and microcrystalline cellulose;

(c) from 0 to 55% w/v of an oily vehicle;

(d) from 0 to 20% w/v of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(e) from 0 to 15% w/v of a viscosity modifying excipient; and

(f) water to make 100% by volume.

2. The x-ray composition of claim 1 wherein said x-ray contrast producing agent is present in an amount of 30 to 200 mg of iodine per ml of the composition.

3. The x-ray contrast composition of claim 1 wherein said oily vehicle constitutes from 0.1 to 25% w/v of the composition.

4. The x-ray contrast composition of claim 1 wherein said surfactant constitutes from 0.1 to 10% of the composition.

5. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising:

(a) from about 40 to 160 mg of iodine per ml of the composition of crystalline contrast agent selected from the group consisting of diatrizoic acid, metrizoic acid, iothalamic acid, trimesic acid, urokonic acid, ioxathalamic acid, tetraiodoterephthalic acid, ioxaglic acid, iodipamide, ethyl-3,5-diacetamido-2,4,6-triiodobenzoate, ethyl-2-(3,5-bis(acetylamino)-2,4,6-triiodo-benzoyloxy)butyrate, and ethyl(3,5-

bis(acetylamino)-2,4,6-triiodobenzoyloxy)-acetate, said crystalline contrast agent having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of from about 0.5 μ to about 100 μ; and

said surface modifier is selected from the group consisting of tetrafunctional block copolymers derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine;

(b) from 0.1 to 4% w/v of a cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose and microcrystalline cellulose;

(c) from 0.1 to 25% w/v of an oily vehicle;

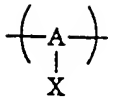
(d) from 0.1 to 10% w/v of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(e) from 0.001 to 4% w/v of a viscosity modifying excipient; and

(f) water to make 100% by volume.

6. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising:

(a) from about 5 to 95% w/v of iodinated, polymeric, water-insoluble beads having a particle size of from about 0.01 to about 1000μ wherein said iodinated polymeric beads comprise a polymer containing repeating units of the formula (I)



I

wherein

A is a repeating organic unit in the backbone chain of the polymer; and

X is an organic moiety containing an iodinated aromatic group and a hydrophilic group, said moiety having an iodine content within the range of from about 40 to about 80 weight percent based on the molecular weight of X;

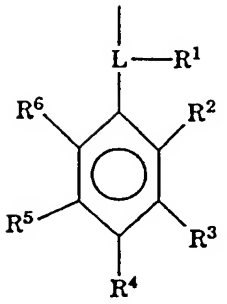
(b) from 0.05 to 10% w/v of a cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose and microcrystalline cellulose;

(c) from 0.1 to 20% w/v of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(d) from 0.001 to 4% w/v of a viscosity modifying excipient; and

(e) water to make 100% by volume.

7. The x-ray contrast composition of claim 6 wherein X represents an organic moiety containing an iodinated aromatic group, said moiety being of the formula



wherein

L represents a linking group selected from the class consisting of ester groups, ether groups, amide groups, thioester groups, carbonate groups, carbamate groups, and sulfide groups; and

each of R^1 to R^6, which may be the same or different, represents hydrogen, an iodine-containing substituent, or a hydrophilic group-containing substituent, with the provisos that (i) the iodine content of X is within the range of from 40 to 80 wt%; and (ii) said hydrophilic group is a member selected from the class consisting of carboxyl groups, sulfo groups, amino groups, salts of the aforementioned carboxyl, sulfo and amino groups, and polyol groups.

8. The x-ray contrast composition of claim 7 wherein said surfactant constitutes from 3 to 7% of the composition.

9. An x-ray contrast composition for oral or retrograde examination of the gastrointestinal tract comprising:

(a) from about 5 to 95% w/v of a barium salt;

(b) from 0.1 to 10% w/v of a cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl

methylcellulose and microcrystalline cellulose;

(c) from 0.1 to 55% w/v of an oily vehicle;

(d) from 0.1 to 20% w/v of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(e) from 0.001 to 15% w/v of a viscosity modifying excipient; and

(f) water to make 100% by volume.

10. The x-ray contrast composition of claim 9 wherein said oily vehicle constitutes from 7 to 15% w/v of the composition.

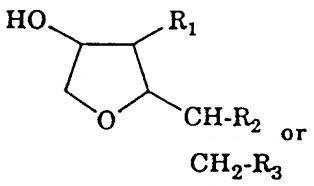
11. The x-ray contrast composition of claim 9 wherein said surfactant constitutes from 3 to 7% of the composition.

12. The x-ray contrast composition of any preceding claim wherein said microcrystalline cellulose has an average particle size of from 0.01 to 100 μ.

13. The x-ray contrast composition of claim 12 wherein said microcrystalline cellulose is about 89 parts microcrystalline cellulose and about 11 parts of sodium carboxymethylcellulose.

14. The x-ray contrast composition of any preceding claim wherein said nonionic surface active agent is selected from the group consisting of carboxylic esters, carboxylic amides, ethoxylated alklyphenols and ethoxylated aliphatic alcohols.

15. The x-ray contrast composition of any of claims 1 to 13 wherein said surfactant is sorbitan ester having the formula:



wherein

$R_1 = R_2 = OH$, $R_3 = R$ for sorbitan monoesters,
$R_1 = OH$, $R_2 = R_3 = R$ for sorbitan diesters,
$R_1 = R_2 = R_3 = R$ for sorbitan triesters,
where R = $(C_{11}H_{23})COO$ for laurate,
$(C_{17}H_{33})COO$ for oleate,
$(C_{15}H_{31})COO$ for palmitate,
$(C_{17}H_{35})COO$ for stearate.

16. The x-ray contrast composition of any of claims 1 to 13 wherein said surface active agent is polyoxyethylene alkyl ether having the formula:

$$CH_3(CH_2)_x(O\text{-}CH_2\text{-}CH_2)_yOH$$

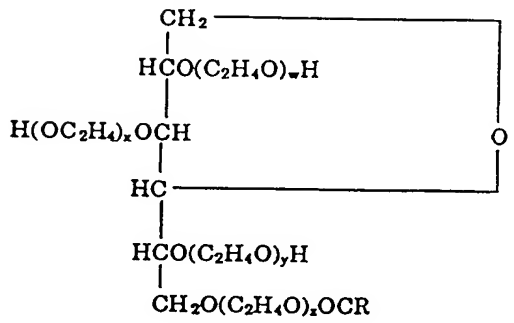
where (x + 1) is the number of carbon atoms in the alkyl chain, typically:

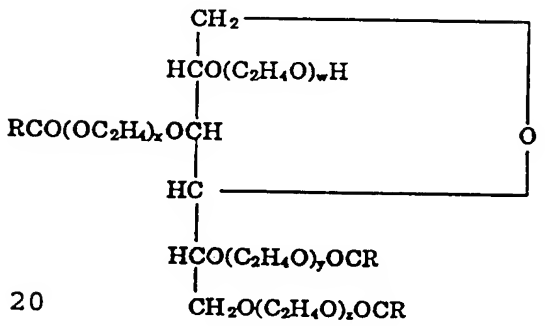
12	lauryl	(dodecyl)
14	myristyl	(tetradecyl)
16	cetyl	(hexadecyl)
18	stearyl	(octadecyl)

and y is the number of ethylene oxide groups in the hydrophilic chain from about 10 to about 60.

17. The x-ray contrast composition of any of claims 1 to 13 wherein said surfactant is polyoxyethylene

sorbitan fatty acid ester of the formulae (1) and (2)





wherein

w+x+y+z = 20

w+x+y+z = 5

w+x+y+z = 4.

18. The x-ray contrast composition of claim 1 for oral or retrograde examination of the gastrointestinal tract comprising:

(a) from about 85 to 120 mg of iodine per ml of the composition of the x-ray contrast producing agent;

(b) from 0.2 to 1% w/v of a cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose and microcrystalline cellulose;

(c) from 7 to 15% w/v of a mineral oil;

(d) from 3 to 7% w/v of a surfactant selected from the group consisting of nonionic, anionic, cationic and zwitterionic surfactants;

(e) from 0.05 to 1% w/v of a viscosity modifying excipient; and

(f) water to make 100% by volume.

19. The x-ray contrast composition of claim 18 wherein the average particle size of said microcrystalline cellulose is from 0.05 to 10μ.

20. A method of carrying out x-ray examination of the gastrointestinal tract of a patient, said method comprises the oral or rectal administration to the patient of an x-ray contrast formulation of any preceding claim.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 95/00386

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB-A-767 788 (SCHERING CO.) 6 February 1957 see page 5, column 1, line 27 - line 31; claims	1
X	CH-A-338 274 (SCHERING CO.) 30 June 1959 see page 2, column 1, line 17 - line 17; claims	1
X	FR-A-2 085 692 (E. R. SQUIBB & SONS, INC.) 31 December 1971 see claims 1-3; example 3	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
29 June 1995	05.07.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Berte, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP-A-0 568 155 (STERLING WINTHROP INC) 3 November 1993 cited in the application see page 6, column 48 - column 58; claims see page 6, column 14 - column 15 see page 7, line 39 - page 8, line 14	1-5, 12-20
A	EP-A-0 568 156 (STERLING WINTHROP INC) 3 November 1993 see page 3, line 55 - page 5, line 34; claims	1-5, 15-20
P,A	EP-A-0 603 922 (STERLING WINTHROP INC) 29 June 1994 see page 6, line 45 - line 48; claims	1-5, 15-20
P,A	EP-A-0 603 923 (STERLING WINTHROP INC) 29 June 1994 see claims	1-20
P,A	EP-A-0 609 589 (STERLING WINTHROP INC) 10 August 1994 see claims	1-20
P,X	EP-A-0 614 668 (STERLING WINTHROP INC) 14 September 1994 see page 5, line 28 - page 7, line 29	1-5, 15-20
P,X	US-A-5 316 755 (ILLIG CARL R ET AL) 31 May 1994 see column 27, line 17 - column 29, line 55; claims	1-5, 15-20
P,X	US-A-5 308 607 (JOSEF KURT A ET AL) 3 May 1994 see column 13, line 47 - column 16, line 9; claims	1-5, 15-20
P,X	US-A-5 330 740 (ILLIG CARL R ET AL) 19 July 1994 see column 6, line 54 - column 8, line 62; claims see column 10, line 40 - line 57	1-5, 15-20
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P,X	US-A-5 310 537 (ILLIG CARL R ET AL) 10 May 1994 see column 5, line 51 - column 8, line 18; claims	1-5, 15-20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US-A-5 310 538 (BACON EDWARD R ET AL) 10 May 1994 cited in the application see column 12, line 65 - column 17, line 4; claims & EP,A,0 614 670	1-5, 15-20
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P,X	WO-A-94 05336 (STERLING WINTROP INC) 17 March 1994 see page 7, line 31 - page 15, line 8; claims	9-20
X	US,A,4 406 878 (CHARLES D. DEBOER) 27 September 1983 cited in the application see column 2, line 14 - line 38 see column 4, line 47 - column 5, line 29; claims	6-8

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INTERNATIONAL SEARCH REPORT

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PCT/GB 95/00386

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/GB 95/00386

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/GB 95/00386

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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